We claim

1. A method for treating a degenerative joint disease, in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount of a compound of formula I

A-B-X-E-F-K-(D)-TIC-G-M-F'-I (I)

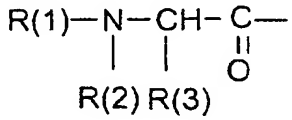
wherein:

A is hydrogen,
(C_1-C_8)-alkyl, (C_1-C_8)-alkanoyl, (C_1-C_8)-alkoxycarbonyl or (C_1-C_8)-alkylsulfonyl, each of which is optionally substituted one, two or three times by carboxyl, amino, (C_1-C_4)-alkyl, (C_1-C_4)-alkyl-amino, hydroxy, (C_1-C_3)-alkoxy, halogen, di-(C_1-C_4)-alkyl-amino, carbamoyl, sulfamoyl, (C_1-C_4)-alkoxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, or each of which is optionally substituted one time by (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkylsulfinyl, (C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfonyl, (C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfinyl, (C_6-C_{12})-aryloxy, (C_3-C_9)-heteroaryl or (C_3-C_9)-heteroaryloxy, and is further optionally substituted one or two times by carboxyl, amino, (C_1-C_4)-alkylamino, hydroxy, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl, (C_1-C_4)-alkyloxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, wherein the heteroaryl is optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl,
(C_3-C_8)-cycloalkyl,
carbamoyl, which is optionally substituted on the nitrogen by (C_1-C_6)-alkyl or (C_6-C_{12})-aryl,
(C_6-C_{12})-aryl, (C_6-C_{12})-aroyl, (C_6-C_{12})-arylsulfonyl, (C_3-C_9)-heteroaryl or (C_3-C_9)heteroaroyl, wherein the heteroaryl, aroyl, arylsulfonyl and heteroaroyl are each independently optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino,

(C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl,

or

of formula II,



II

wherein

R(1) is hydrogen,

(C_1-C_8)-alkyl, (C_1-C_8)-alkanoyl, (C_1-C_8)-alkoxycarbonyl or (C_1-C_8)-alkylsulfonyl, each of which is optionally substituted one, two or three times by carboxyl, amino, (C_1-C_4)-alkyl, (C_1-C_4)-alkyl-amino, hydroxy, (C_1-C_3)-alkoxy, halogen, di-(C_1-C_4)-alkyl-amino, carbamoyl, sulfamoyl, (C_1-C_4)-alkoxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, or each of which is optionally substituted one time by (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkylsulfinyl, (C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfonyl, (C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfinyl, (C_6-C_{12})-aryloxy, (C_3-C_9)-heteroaryl or (C_3-C_9)-heteroaryloxy, and is further optionally substituted one or two times by carboxyl, amino, (C_1-C_4)-alkylamino, hydroxy, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl, (C_1-C_4)-alkyloxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, wherein the heteroaryl is optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl,

(C_3-C_8)-cycloalkyl,

carbamoyl, which is optionally substituted on the nitrogen by (C_1-C_6)-alkyl or (C_6-C_{12})-aryl,
or
(C_6-C_{12})-aryl, (C_6-C_{12})-aroyl, (C_6-C_{12})-arylsulfonyl, (C_3-C_9)-heteroaryl or (C_3-C_9)heteroaroyl, wherein the heteroaryl, aroyl, arylsulfonyl and heteroaroyl are each independently optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl,

R(2) is hydrogen or methyl,

R(3) is hydrogen or (C_1-C_6)-alkyl, wherein the alkyl is optionally monosubstituted by amino, substituted amino, hydroxy, carbamoyl, guanidino, substituted guanidino, ureido, mercapto, methyl-mercapto, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-nitrophenyl, 4-methoxyphenyl, 4-hydroxyphenyl, phthalimido, 4-imidazolyl, 3-indolyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl or cyclohexyl, wherein the substituted amino is –NH-A'- and the substituted guanidino is–NH-C(NH)-NH-A'-, wherein A' is

hydrogen,
(C_1-C_8)-alkyl, (C_1-C_8)-alkanoyl, (C_1-C_8)-alkoxycarbonyl or (C_1-C_8)-alkylsulfonyl, each of which is optionally substituted one, two or three times by carboxyl, amino, (C_1-C_4)-alkyl, (C_1-C_4)-alkyl-amino, hydroxy, (C_1-C_3)-alkoxy, halogen, di-(C_1-C_4)-alkyl-amino, carbamoyl, sulfamoyl, (C_1-C_4)-alkoxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, or each of which is optionally substituted one time by (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkylsulfinyl, (C_6-

C_{12})-aryl-(C_1-C_4)-alkylsulfonyl, (C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfinyl, (C_6-C_{12})-aryloxy, (C_3-C_9)-heteroaryl or (C_3-C_9)-heteroaryloxy, and is further optionally substituted one or two times by carboxyl, amino, (C_1-C_4)-alkylamino, hydroxy, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl, (C_1-C_4)-alkyloxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, wherein the heteroaryl is optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl,

(C_3-C_8)-cycloalkyl,

carbamoyl, which is optionally substituted on the nitrogen by (C_1-C_6)-alkyl or (C_6-C_{12})-aryl,

or

(C_6-C_{12})-aryl, (C_6-C_{12})-aroyl, (C_6-C_{12})-arylsulfonyl, (C_3-C_9)-heteroaryl or (C_3-C_9)heteroaroyl, wherein the heteroaryl, aroyl, arylsulfonyl and heteroaroyl are each independently optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl;

B is Arg, Lys, Orn, 2,4-diaminobutyroyl or L-homo-arginine, wherein the amino or the guanidino group of the side chain of Arg, Lys, Orn, 2,4-diaminobutyroyl or L-homo-arginine is independently optionally substituted by

hydrogen,

$(C_1$-$C_8)$-alkyl, $(C_1$-$C_8)$-alkanoyl, $(C_1$-$C_8)$-alkoxycarbonyl or $(C_1$-$C_8)$-alkylsulfonyl, each of which is optionally substituted one, two or three times by carboxyl, amino, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkyl-amino, hydroxy, $(C_1$-$C_3)$-alkoxy, halogen, di-$(C_1$-$C_4)$-alkyl-amino, carbamoyl, sulfamoyl, $(C_1$-$C_4)$-alkoxycarbonyl, $(C_6$-$C_{12})$-aryl or $(C_6$-$C_{12})$-aryl-$(C_1$-$C_5)$-alkyl, or each of which is optionally substituted one time by $(C_3$-$C_8)$-cycloalkyl, $(C_1$-$C_4)$-alkylsulfonyl, $(C_1$-$C_4)$-alkylsulfinyl, $(C_6$-$C_{12})$-aryl-$(C_1$-$C_4)$-alkylsulfonyl, $(C_6$-$C_{12})$-aryl-$(C_1$-$C_4)$-alkylsulfinyl, $(C_6$-$C_{12})$-aryloxy, $(C_3$-$C_9)$-heteroaryl or $(C_3$-$C_9)$-heteroaryloxy, and is further optionally substituted one or two times by carboxyl, amino, $(C_1$-$C_4)$-alkylamino, hydroxy, $(C_1$-$C_4)$-alkoxy, halogen, di-$(C_1$-$C_4)$-alkylamino, carbamoyl, sulfamoyl, $(C_1$-$C_4)$-alkyloxycarbonyl, $(C_6$-$C_{12})$-aryl or $(C_6$-$C_{12})$-aryl-$(C_1$-$C_5)$-alkyl, wherein the heteroaryl is optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, $(C_1$-$C_4)$-alkylamino, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, halogen, di-$(C_1$-$C_4)$-alkylamino, carbamoyl, sulfamoyl or $(C_1$-$C_4)$-alkoxycarbonyl,

$(C_3$-$C_8)$-cycloalkyl,

carbamoyl, which is optionally substituted on the nitrogen by $(C_1$-$C_6)$-alkyl or $(C_6$-$C_{12})$-aryl,

or

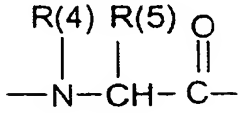
$(C_6$-$C_{12})$-aryl, $(C_6$-$C_{12})$-aroyl, $(C_6$-$C_{12})$-arylsulfonyl, $(C_3$-$C_9)$-heteroaryl or $(C_3$-$C_9)$heteroaroyl, wherein the heteroaryl, aroyl, arylsulfonyl and heteroaroyl are each independently optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, $(C_1$-$C_4)$-alkylamino, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, halogen, di-$(C_1$-$C_4)$-alkylamino, carbamoyl, sulfamoyl or $(C_1$-$C_4)$-alkoxycarbonyl;

X is of formula IIIa or IIIb

G'-G'-Gly (IIIa)

G'-NH-$(CH_2)_n$-CO (IIIb),

wherein G' independently of one another is of formula IV



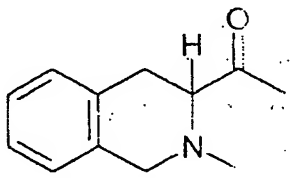
IV

wherein R(4) and R(5) together with the atoms they connect to form a heterocyclic mono-, bi- or tricyclic ring having 2 to 15 carbon atoms, and n is 2 to 8;

E is phenylalanine optionally substituted by halogen in the 2-, 3-or 4-ring position, tyrosine, O-methyltyrosine, 2-thienylalanine, 2-pyridylalanine or naphthylalanine;

F is covalent bond, or neutral, acidic or basic aliphatic or aromatic amino acid, which is optionally substituted in the side chain;

(D)-TIC is of formula V



V

G is G' or a covalent bond;

F' is covalent bond, $-NH-(CH_2)_n-$ wherein n is 2 – 8, or basic amino acid Arg or Lys in the L or D form, wherein the guanidino group or amino group of the side chain of the Arg or Lys is optionally substituted by

hydrogen,

(C_1-C_8)-alkyl, (C_1-C_8)-alkanoyl, (C_1-C_8)-alkoxycarbonyl or (C_1-C_8)-alkylsulfonyl, each of which is optionally substituted one, two or three times by carboxyl, amino, (C_1-C_4)-alkyl, (C_1-C_4)-alkyl-amino, hydroxy, (C_1-C_3)-alkoxy, halogen, di-(C_1-C_4)-alkyl-amino, carbamoyl, sulfamoyl, (C_1-C_4)-alkoxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, or each of which is optionally substituted one time by (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkylsulfinyl, (C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfonyl, (C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfinyl, (C_6-C_{12})-aryloxy, (C_3-C_9)-heteroaryl or (C_3-C_9)-

heteroaryloxy, and is further optionally substituted one or two times by carboxyl, amino, (C_1-C_4)-alkylamino, hydroxy, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl, (C_1-C_4)-alkyloxycarbonyl, (C_6-C_{12})-aryl or (C_6-C_{12})-aryl-(C_1-C_5)-alkyl, wherein the heteroaryl is optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl,
(C_3-C_8)-cycloalkyl,
carbamoyl, which is optionally substituted on the nitrogen by (C_1-C_6)-alkyl or (C_6-C_{12})-aryl,
or
(C_6-C_{12})-aryl, (C_6-C_{12})-aroyl, (C_6-C_{12})-arylsulfonyl, (C_3-C_9)-heteroaryl or (C_3-C_9)heteroaroyl, wherein the heteroaryl, aroyl, arylsulfonyl and heteroaroyl are each independently optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl;

I is -OH, $-NH_2$ or NHC_2H_5;

K is covalent bond or $-NH-(CH_2)_x-CO$, wherein x is 1 to 4; and

M is covalent bon, or neutral, acidic or basic aliphatic or aromatic amino acid, which is optionally substituted in the side chain;

or its physiologically tolerable salts thereof.

2. The method according to claim 1, wherein

B is Arg, Orn or Lys,
wherein the guanidino group or the amino group of the side chain is each independently optionally substituted by (C_1-C_8)-alkanoyl, (C_6-C_{12})-aroyl, (C_3-C_9)-heteroaroyl, (C_1-C_8)-alkylsulfonyl or (C_6-C_{12})-arylsulfonyl, wherein the aroyl, arylsulfonyl and heteroaroyl are each independently optionally substituted one, two, three or four times by carboxyl, amino, nitro, hydroxy, cyano, (C_1-C_4)-alkylamino, (C_1-C_4)-alkyl, (C_1-

C_4)-alkoxy, halogen, di-(C_1-C_4)-alkylamino, carbamoyl, sulfamoyl or (C_1-C_4)-alkoxycarbonyl;

E is phenylalanine, 2-chlorophenylalanine, 3-chloro-phenylalanine, 2-fluorophenylalanine, 3-fluorophenyl-alanine, 4-fluorophenylalanine, tyrosine, O-methyl-tyrosine or β-(2-thienyl)alanine;

K is covalent bond; and

M is covalent bond.

3. The method according to claim 1, wherein:

A is hydrogen, (D)- or (L)-H-Arg, (D)- or (L)-H-Lys or (D)- or (L)-H-Orn;

B is Arg, Orn or Lys,
wherein the guanidino group or the amino group of the side chain is optionally substituted by hydrogen, (C_1-C_8)-alkanoyl, (C_6-C_{12})-aroyl, (C_3-C_9)-heteroaroyl, (C_1-C_8)-alkylsulfonyl or (C_6-C_{12})-arylsulfonyl, wherein the aroyl, arylsulfonyl and heteroaroyl are each independently optionally substituted one, two, three or four times by methyl, methoxy or halogen;

X is Pro-Pro-Gly, Hyp-Pro-Gly or Pro-Hyp-Gly;

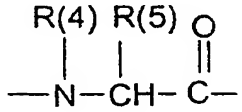
E is Phe or Thia;

F is Ser, Hser, Lys, Leu, Val, Nle, Ile or Thr;

K is covalent bond

M is covalent bond

G is of the formula IV,



IV

wherein R(4) and R(5) together with the atoms they connect to form pyrrolidine, piperidine, tetrahydro-isoquinoline, cis- or trans-decahydroisoquinoline, cis-endo-octahydroindole, cis-exo-octahydro-indole, trans-octahydroindole, cis-endo-, cis-exo-, trans-octahydrocyclopentano[b]pyrrole, or hydroxyproline;

F' is Arg; and

I is OH.

4. The method according to claim 1, wherein the compound of the formula I is
H-(D)-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH,
H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH,
H-(D)-Arg-Arg-Pro-Hyp-Gly-Phe-Ser-(D)-Tic-Oic-Arg-OH,
H-(D)-Arg-Arg-Hyp-Pro-Gly-Phe-Ser-(D)-Tic-Oic-Arg-OH or
H-(D)-Arg-Arg-Pro-Pro-Gly-Phe-Ser-(D)-Tic-Oic-Arg-OH.

5. The method according to claim 1, wherein the compound of the formula I is D-arginyl-L-arginyl-L-prolyl-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-(3R)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-(2S,3aS,7aS)-octahydro-1H-indole-2-carbonyl-L-arginine.

6. The method according to claim 1, wherein the degenerative joint disease is osteoarthrosis, spondyloses or cartilage atrophy after immobilization.

7. The method according to claim 1, wherein the administration is carried out by subcutaneous, intraarticular, intraperitoneal or intravenous injection or transdermal administration.